UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/056,072	04/07/1998	HERVE BAZIN	61750221	4832

7590 08/10/2004

CARELLA BYRNE BAIN GILFILLAN CECCHI
STEWART & OLSTEIN
6 BECKER FRAM ROAD
ROSELAND, NJ 07068

EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/056,072	BAZIN ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission, filed on 2/20/04, has been entered.

Claims 30-43 are pending and being acted upon.
Claims 1-29 have been canceled previously.

2. The Decision on Appeal by the Board of Patent Appeals and Interferences, mailed 7/31/03, is acknowledged.

3. As pointed out previously, **a substitute specification is required because the numerous entries to be amended in the specification, filed 1/4/99 (Paper No. 6)**. The substitute specification filed must be accompanied by a statement that it contains no new matter. Such statement must be a verified statement if made by a person not registered to practice before the Office.

It does not appear that applicant has provided a substitute specification at this time.

4. **Again, applicant is required to comply with sequence rules as indicated in the previous Office Action (Paper No. 4) and reiterated herein.**

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821-1.825, however, this application fails to comply with the requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

The following procedure is to be used for cases that contain the same sequence disclosure as the parent. The applicant need not submit a new computer readable from of the Sequence Listing in this divisional. However, (1) the specification must contain a paper copy of the Sequence Listing, (2) applicant must request in writing that the CRF in the parent case be used to prepare a file for the offspring and (3) applicant must submit a statement that the paper copy of the Sequence Listing in the offspring is identical to the computer readable form submitted in the parent case.

5. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Applicant is required to amend the first line of the specification to update the status and relationship of the priority documents.

6. As pointed out previously, it is apparent that the LO-CD2a antibody/hybridoma is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line / hybridoma which produces this antibody (claims 30-44). See 37 CFR 1.801-1.809.

Given that the deposit requirements for the LO-CD2a antibody/hybridoma produced by the cell line deposited as ATCC HB 11423 have been satisfied and claimed in U.S. Patent No. 5,730,979; the requirement for the LO-CD2a antibody/hybridoma in this application is not necessary.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 30-32, 35-37, 39 and 40 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Xia et al. (Rat Hybridomas and Rat Monoclonal Antibodies, 1990) for the reasons of record .

Xia et al. teach the LO-CD2a-specificity, including hybridomas and methods of making said antibodies and hybridomas of the instant invention (see entire document and page 312 for example).

See the Examiner's Answer, mailed 8/24/00, for a more complete analysis of applicant's arguments and the examiner's rebuttal.

10. Claims 30-43 are rejected under 35 U.S.C. § 103 as being unpatentable over Xia et al. (Rat Hybridomas and Rat Monoclonal Antibodies, 1990) in view of Queen et al. (U.S. Patent No. 5,530,101) or Newman et al. (U.S. Patent No. 5,658,570) and in further view of Guckel et al. (J. Exp. Med., 1991) OR Bromberg et al. (Transplant., 1991) OR Hafler et al. (J. Immunol., 1988) OR Chavin et al. (Transplant., 1992) OR Faustman (U.S. Patent No. 5,283,058).

Claims 30-43 stand rejected under 35 U.S.C. § 103 as being unpatentable over Xia et al. (Rat Hybridomas and Rat Monoclonal Antibodies, 1990) in view of Queen et al. (U.S. Patent No. 5,530,101) or Newman et al. (U.S. Patent No. 5,658,570) and in further view of Guckel et al. (J. Exp. Med., 1991) OR Bromberg et al. (Transplant., 1991) OR Hafler et al. (J. Immunol., 1988) OR Chavin et al. (Transplant., 1992) OR Faustman (U.S. Patent No. 5,283,058).

The instant claims are drawn to antibodies that bind the LO-CD2 specificity, including chimeric and humanized antibodies, as well as cell that produced said antibodies and methods of making said antibody.

Xia et al. provides a number of phenotypic and functional characteristics that are associated with the LO-CD2a specificity (see entire document). Also, Xia et al. distinguishes the LO-CD2a specificity from other CD2-specific antibodies and clearly discloses that this specificity binds a different epitope from other CD2-specific antibodies (for example, see page 320, paragraphs 1-3). It would have been expected at the time the invention was made that different antibodies would recognize the same conformational epitope, which is the LO-CD2 epitope in the instant case. The prior art clearly set forth numerous features that characterize and enable one of skill in the art at the time the invention was made to make an antibody that binds to the same LO-CD2 epitope specificity as claimed. Xia et al. Differs from the instant claims by not disclosing chimeric or humanized antibodies per se.

Queen et al. teaches the art-known procedures at the time the invention was made to produce chimeric antibodies starting from hybridoma and antibody producing cells (see entire document)..

Similarly, Newman et al. teach the generation of recombinant antibodies including CD2-specific antibodies for various diagnostic and therapeutic uses (see entire document).. While it is noted that Newman et al. teaches the use of Old World Monkey portions in the derivation of recombinant antibodies, this reference clearly recognizes the derivation of chimeric and humanized antibodies at the time the invention was made and that CD2 was a desired specificity at the time the invention was made.

One of ordinary skill in the art at the time the invention was made would have generated chimeric or humanized antibodies in order to reduce immunogenicity while retaining high binding affinity for diagnostic and therapeutic purposes as well as the appropriate vectors, host cells, etc. to accomplish the engineering of chimeric and humanized antibodies (see entire documents). Therefore, Queen et al. OR Newman et al. teach that immunoglobulin gene structure and organization were well understood in the art at the time the claimed invention was made and that strategies for cloning the DNAs encoding immunoglobulin variable regions genes were well established in the art at the time the claimed invention was made, as were methods for the production of DNA constructs comprising expression vectors containing DNAs encoding immunoglobulin variable regions. Queen et al. AND Newman et al. differ from the claimed invention by not

teaching the LO-CD2a specificity per se, the ordinary artisan would have been motivated to apply the teachings of Queen et al. OR Newman et al. to enable the isolation and construction of chimeric and humanized antibodies that bind the LO-CD2a specificity.

In addition to the LO-CD2a specificity, the instant claims also encompass antibodies that elicit alloantigen specific unresponsiveness. Guckel et al., Bromberg et al., Hafler et al., Chavin et al. and Faustman all teach the art-known potent inhibition of immune responses by blocking or modulating T cell surface receptors such as CD2 that are important in adhesion receptor-signaling (see entire documents, particularly the Introductions and Discussions).

Guckel et al. teach the ability of rat anti-CD2 antibodies to induce T cell unresponsiveness in vitro and in vivo in mice (see entire document). CD2-specific antibody inhibition of transplants and autoimmunity is taught (page 965, column 2, paragraph 2). Guckel et al. Also teach that CD2 modulation was dose and time dependent, whereby a single dose of 0.1 – 5 mg purified antibody resulted in maximal modulation within 24 hours (see page 964, column 1, paragraph 1).

Bromberg et al. teach that anti-CD2 antibodies alter cell-mediated immunity, such as cntact sensitivity and CTL responses in vivo by altering the array of cell surface receptors and subsequent responses to antigenic challenge (see entire document). Additonal experiments showed a well-defined dose-response relatiohsip between the amount of anti-CD2 admininsted and subsequent immunosuppression (see Abstract on page 219, column 1). Bromberg et al. also teach the potent immunosuppressive properties of anti-CD2 antibodies for murine allografts and xenografts as well as for primate skin and renal allografts (page 224, column 1, paragraph 1).

Hafler et al. teach that anti-CD2 antibodies inhibit T cell responses in human patients with progressive multiple sclerosis (see entire document). In addition to in vivo effects, the in vivo anti-T cell antibodies infusions could be immunosuppressive as determined by in vitro assays (page 136-137, overlapping paragraph). Patients received 0.2 mg /kg antibody in pharmaceutical compositions (see Materials and Methods mAb Infusions). Hafler et al. also teach that T cell-specific antibodies have been used successfully as immunosuppressive reagents in transplant rejections and autoimmune diseases (see Introduction).

Chavin et al. teaches the efficacy of treating allografts and xenografts in vivo with CD2-specific antibodies (see entire document, particularly the Introduction and Discussion). Prolonged allograft survival correlated with suppression of both CTL and NK activity (page 290, column 1, paragraph 3 and Table 2). Chavin et al. teach that anit-human CD2 antibodies have been used in primate models of allografting and have ben found to be effective immunosuppressive agent and that antihuman CD2 antibody may be quite potent in humans (see page 289, column 2, paragraph 1). Previous and current data demonstrate that anti-CD2 antibodies affects a variety of CD4/CD8 T cell dependent response inducing CTL, contact sensitivity, proliferation, IgG responses, tumor immunity, natural killer cytotoxicity and allograft rejection (see page 290, column 1, paragraph 2). Here, Chavin et al. concludes by stating that the ability of anti-CD2 antibodies to suppress lymphocyte precursors and T and non-T cell responses supports its use for induction therapy in transplantation (page 290, last paragraph).

Faustman teaches methods of inhibiting the rejection of allografts and xenografts with T cell-specific antibodies and antibody fragments including the CD2-specificity (see entire document, including column 5, paragraph 1). Such methods of inhibiting rejection include modifying, eliminating and masking an antigen on the surface of a cell (see entire document, including Abstract). In addition, Faustman teaches perfusion with antibodies is carried out by conventional techniques (see column 10, paragraph 1).

Given the in vitro and in vivo observations of potent blocking of various T cell mediated immune responses, including the induction of antigen specific unresponsiveness,

Given the binding and inhibitory properties of the LO-CD2a-specific antibody, including strongly depressing antigen-induced lymphocyte activation and proliferation taught by Xia et al.; one of ordinary skill in the art would have motivated to employ the LO-CD2a in various biological, diagnostic and therapeutic modalities, as taught by the prior art above. It is noted that Xia et al. acknowledged that the ordinary artisan was motivated to employ monoclonal antibodies as attractive reagents for clinical therapeutic use at the time the invention was made (see Introduction on page 310).

Given the teachings of Guckel et al., Bromberg et al., Hafler et al., Chavin et al. and Faustman of the art-known potent inhibition of immune responses both in vitro and in vivo by blocking or modulating CD2, one of ordinary skill in the art would have had a reasonable expectation of success that the binding and functional properties of the LO-CD2a antibody specificity would have been consistent with such potent antigen-specific immune responses of the prior art anti-CD2 inhibitory antibodies. Given the prior art teachings of antibody compositions for both in vitro and in vivo regimens employing, characterizing and testing antibodies, including anti-CD2 antibodies, the ordinary artisan would have been motivated to place antibodies with the LO-CD2a specificity in composition form, including in amounts effective to inhibit T cell mediated immune responses, as practiced by the prior art (e.g. see Guckel et al., Bromberg et al., Hafler et al., Chavin et al. and Faustman). Also, note that the claimed compositions do not recite a specific amount of anti-LO-CD2a antibodies. It is noted that page 18, paragraph 1 of the instant specification discloses that the scope of the invention is not limited by amounts such as 1 mg. The prior art antibodies including the LO-CD2a antibody specificity do inhibit T cell activation, which is consistent with amounts effective to inhibit T cell mediated immune responses.

It would have prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to generate CD2-specific antibodies including the LO-CD2-specific antibodies to characterize the CD2 specificity and to target said specificity for various biological, diagnostic and therapeutic modalities, as taught by the prior art. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

See the Examiner's Answer, mailed 8/24/00, for a more complete analysis of applicant's arguments and the examiner's rebuttal.

11. The terminal disclaimer filed on 4/29/96 (Paper No. 14), disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 5,264,554 has been reviewed and is accepted

The terminal disclaimer filed on 2/20/04 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 5,730,979 has been reviewed and is accepted

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
August 9, 2004